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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/624,942	07/21/2003	Marco Pappagallo	05986/100K504-US1	7691

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EXAMINER	
KIM, JENNIFER M	

ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
05/12/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/624,942	PAPPAGALLO, MARCO	
	Examiner	Art Unit	
	JENNIFER MYONG M. KIM	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/17/2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 11* is/are rejected.

7)☒ Claim(s) *10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 17, 2009 has been entered.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-8 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treating chronic spinal mechanical pain with the employment of the **specific bisphosphonates (i.e. pamidronate, zoledronic acid)** does not reasonably provide enablement for the treatment of the pain with **"a bisphosphonate"** . The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

3. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, predictability of the prior art, state of the prior art and the amount of experimentation necessary. All of the **Wands factors** have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: All of the rejected claims are drawn to a method of treating chronic spinal mechanical pain which comprises intravenously administering to a subject in need of chronic spinal mechanical pain relief an effective amount for relieving chronic spinal mechanical pain of a bisphosphonate, wherein the bisphosphonate provides prolonged pain relief such that the subject treated with above compounds does not contract pain.

Breath of the Claims: The complex of nature of the claims greatly exacerbated by breath of the claims. The claims encompass treatment of a chronic spinal mechanical pain in humans with **a bisphosphonate** which has potentially many different effects in pain treatment (i.e. toxicity). Each of which may or may not be addressed by the administration of the claimed compounds.

Guidance of the Specification: The guidance given by the specification as to how one would administered the claimed compounds (bisphosphonates) to a subject in order to actually treat chronic spinal mechanical pain is minimal. All of

the guidance provided by the specification is directed towards the specific bisphosphonate (i.e. pamidronate and zoledronic acid) rather than a bisphosphonate.

Working Examples: All of the working examples provided by the specification are directed towards the specific bisphosphonate (i.e. pamidronate and zoledronic acid) rather than a bisphosphonate.

State of the Art: While the state of the art is relatively high with regard to treatment of chronic spinal mechanical pain with employment of the specific bisphosphonates, the state of the art with regard to employment of any bisphosphonate to treat such disorders is underdeveloped. The specification discloses that Goicoechea et al. (1999) report that alendronate was able to reduce visceral pain but the effective doses were close to those that induce toxicity. The specification also disclose that Bonabello et al. (2001) teaches that etidronate and alendronate produce an analgesic effect only at the highest dose tested and neither of two references studied any long term pain antinociceptive effects resulting from the administration of a bisphosphonate. To the extent that the instant claims are drawn to treatment of chronic mechanical pain with **a bisphosphonate**, which is highly speculative, a greater amount of evidence is required to show its operability in humans.

Predictability of the Art: The lack of significant guidance from the specification or prior art with regard to the actual treatment of chronic spinal mechanical pain with the employment of any bisphosphonate in a human subject addition to the

disclosure in the specification that no studies per performed for the long term pain with the claimed broad genus of a bisphosphonate makes practicing the claimed invention unpredictable in terms of employment of any bisphosphonate.

The amount of Experimentation Necessary*:* In order to practice claimed invention, one of skilled in the art would have to first envision a combination of appropriate pharmaceutical carrier, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system for one of the claimed a bisphosphonate and test the combination in the model system to determine whether or not the combination is effective for the treatment of chronic spinal mechanical pain. If unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regarding employment of a bisphosphonate with treatment of chronic spinal mechanical pain, one of skill in the art would have to then either envision a modification of the first combination of pharmaceutical compound, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above, and test the system again. If again unsuccessful, which is likely given the lack of significant guidance form the specification of prior art regarding employment of a bisphosphonate for the treatment of chronic spinal mechanical pain, the entire, unpredictable process would have to be repeated until successful. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to treat chronic spinal

mechanical pain in a subject by administration of one of the claimed a bisphosphonate.

Therefore, a method of treating chronic spinal mechanical pain which comprises intravenously administering to a subject in need of chronic spinal mechanical pain relief an effective amount for relieving chronic spinal mechanical pain of **a bisphosphonate**, wherein the bisphosphonate provides prolonged pain relief is not considered to be enabled by the instant specification.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-9 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Geusens et al. (2001) of record.

Geusens et al. teach that an 18-year-old boy presented with extreme back pain as the result of multiple vertebral fractures was treated with intermittent intravenous bisphosphonate such as **pamidronate**. (abstract). Geusens et al. teach that intermittent IV infusions of pamidronate were given at dose of 30mg infusion, 300 mg in total over 9 month. (page 390 right-hand column first sentence originated from left-hand column, bottom). The boy progressively recovered from **back pain** and is now, at age 20, fully ambulant. (abstract).

Geusens et al. do not teach the specific chronic spinal mechanical pain as being any back pain lasting more than twelve weeks which is not caused by cancer, or an

osteoporotic compression fracture as defined in the specification page 7, and the treatment comprising providing prolonged pain relief.

However, it would have been obvious to one of ordinary skill in the art to employ pamidronate for the treatment of any back pain regardless of the cause because the effectiveness of pamidronate in pain management is well taught by Geusens et al. One would have been motivated to employ pamidronate for the treatment of any pain regardless of its cause in order to achieve the beneficial analgesic effect of pamidronate in the patient disclosed by Geusens et al. who progressively recovered from suffering from an extreme back pain with the treatment comprising pamidronate. There is a reasonable expectation of successfully treating any pain particularly back pain regardless of a cause because pamidronate treatment in the patient disclosed by Genuses recovered from the back pain with administration of pamidronate, therefore, the analgesic effect of pamidronate would be retained and it would be effective of treating pain regardless of the etiology of how the patient conceived pain. With regard to the limitation of providing prolonged pain relief set forth in claim 1, such is obvious because Geusens et al. teach that intermittent IV infusions of pamidronate were given at dose of 30mg infusion, 300 mg in total over 9 month. Genusens et al's duration of therapy over 9 month comprising administration of pamidronate obviously provided "prolonged" pain relief because the boy progressively recovered from **back pain over 9 month therapy** and is now, fully ambulant.

For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 35 U.S.C. 103.

None of the claims are allowed.

Response to Arguments

Applicant's arguments filed February 17, 2009 have been fully considered but they are not persuasive. Applicant argues that the patient in Geusens did have an improvement in his pain, but other treatments he received, alone or in combination, can account for this improvement and that bisphosphonates including pamidronate are only mentioned in Geusens in relation to bone density. Applicant further argues that the instant claims are directed to administering bisphosphonate for the relief of chronic spinal mechanical pain and no combination of the references teaches this feature. This is not found to be persuasive because Geusens et al. teaches that other treatments such as calcium and vitamin D administered to Geusens' patient since the start of the glucocorticoids. However, these other treatments resulted hospitalizing the pain due to the severity of the back pain. Therefore, one of ordinary skill in the art would immediately envision that those "other" treatments were ineffective in treating back pain in the patients disclosed by Geusens. Geusens et al. also teaches the analgesics and

nonsteroidal anti-inflammatory drugs relieved pain but partially; calcitonin was added but again only partial effects on pain. Lastly, the patient was treated pamidronate and he progressively recovered from back pain and no longer takes any glucocorticoids. Applicant argument regarding Urban reference is moot in view of the second Declaration of Dr. Marco Pappagallo prompted to withdraw Urban as reference. Therefore, again, those "other" treatments were ineffective in treating back pain and did not contribute to the analgesic effect of pamidronate. Further, the effectiveness of pamidronate having antinociceptive effect was well known in the art at the time the invention was made as disclosed in the instant specification page 4. Applicants admit that in 2001, Bonabello et al. observed a dose dependent antinociception with pamidronate. Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

Allowable Subject Matter

Claim 10 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Communication

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER M. KIM whose telephone number is (571)272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JENNIFER M KIM/

Primary Examiner, Art Unit 1617

Jmk
May 11, 2009